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Dear Christopher,

Response to Appraisal Consultation Document:
Continuous subcutaneous insulin infusion for the treatment of diabetes mellitus (review of technology appraisal guidance 57)

Thank you for the opportunity to respond to the preliminary recommendations on the use of insulin pumps. We recognise this is, in the main, a very positive outcome for individuals with type 1 diabetes, and especially children, providing greater access to this valuable technology.

Whilst we concur with the main conclusions of the Committee, we do however wish to raise several issues for further consideration at the Second Appraisal Committee meeting in January. These issues, listed below, address the ACD question; ***Are the summaries reasonable interpretations of the evidence?***

The four issues we propose for further consideration are:

1. The potential confusion of "mean baseline" to "minimum" HbA1c level
2. The use of the term "adequate control"
3. Relative and absolute lack of insulin in patients with type 2 diabetes
4. Clarity on the age cut-off for paediatrics

1) Potential confusion of "mean baseline" and "minimum" HbA1c level

Recommendation 1.3 states that one parameter potentially indicating insulin pump use is that;

> *"It has been impossible for the individual to maintain a haemoglobin A1c (HbA1c) level of less than 8.5%"*.

We are unclear how the **minimum** threshold of 8.5% has been arrived at. The economic analyses submitted by both the Assessment Team and as part of the industry submission demonstrated that insulin pump therapy in populations with a **minimum** threshold of 7.5% would be cost effective, taking in to consideration improved glyceamic control, the reduction in hypoglycaemic events and related quality of life benefits. The mean HbA1c **baseline**

values used by industry and the Assessment Team were 8.1% and 8.8%, respectively. The appraisal committee appears to have taken the **mean** starting "baseline" value as the **absolute minimum** value acceptable. Clearly shifting the **minimum** threshold to 8.5% would shift the population **mean** HbA1c up significantly. As indicated in the industry submission, epidemiological data from the HODaR database (Cardiff) indicates that in the population of type 1 diabetes whose HbA1c is >7.5%, the population mean HbA1c is 10.1%. Therefore, if NICE restricts access to those over 8.5%, the population mean will be significantly higher.

> **Summary:** We request the Committee consider lowering the minimum HbA1c level to 7.5% as an indictor for the option of insulin pump therapy.

2) The use of the term "adequate control"

Without prejudice of the issue above, in Recommendation 1.2 – the wording;

> *"MDI therapy (including, if appropriate, the use of long-acting insulin analogues) has failed to provide adequate control of diabetes mellitus as defined in section 1.3"*

We recommend that the word "adequate" be deleted, and the sentence read, "*MDI therapy has failed to provide control of diabetes mellitus as defined in 1.3*." We request this because 1.3 would effectively define "adequate control" as an HbA1c less than 8.5%. This is clearly not "adequate control" by any clinical definition. Whilst we propose that the evidence supports the use of insulin pumps as an option for anyone who cannot be controlled at an HbA1c <7.5%, if the Committee persists with 8.5% as the access threshold for insulin pump therapy, it should not imply that an HbA1c level below that is "adequate control".

> **Summary:** We request the word "adequate" be dropped from paragraph 1.2.

3) Relative and Absolute lack of insulin in Type 2 Diabetics

We wish to draw to the Committee's attention the brief summary in Paragraph 2.1. The summary states;

> *"Type 2 diabetes mellitus is characterised by insulin resistance and is often associated with obesity. In type 2 diabetes mellitus, the pancreas initially responds by increasing insulin production, but over time this excess production cannot be maintained, leading to a* ***relative lack*** *of insulin."*

Though insulin resistance is clearly a very important contributing factor in the development of type 2 diabetes, the pathophysiologic description above does not take into account the well-described insulin secretory defect which results not only in a "**relative**" - but with time - in an **"absolute"** reduction of insulin. The United Kingdom Prospective Diabetes Study (UKPDS) clearly demonstrated that pancreatic islet function was about 50% of normal at the time of diagnosis and continued to decline with increasing duration of diabetes. This progressive decline occurred regardless of the treatment patients received.[1,2]

From a clinical perspective, patients with type 2 diabetes who are at the "end of the spectrum" with regards to beta-cell function (having an absolute insulin deficiency), are often very similar to patients with type 1 diabetes. These are patients that if not well controlled on multiple daily injections of insulin, can often benefit significantly from insulin pump therapy.

Summary: We request the Committee consider permitting access to uncontrolled patients with type 2 diabetes failing on MDI where it is clinically evident that the patient has absolute insulin deficiency.

4) Clarification on age cut-off for paediatrics

With respect to the definition of the child population in section 1.1, we believe that the wording should be changed from "as a treatment option for children younger than 11 years" to "as a treatment option for children up to 12 years of age". This would give clarity to pre and post secondary school children. The wording in section 1.2 would need to be amended accordingly to children older than 12 years of age.

Minor Comments

Finally, we have two comments on the response to our comments on the Assessment Report. We recognise the Assessment team has not accepted our cost of a severe hypo event. However they have not acknowledged the misquoted data referenced from TA53. We request this be acknowledged in any future monograph; otherwise the misquote could become fact in future citations. Furthermore, there is no acknowledgement of the additional evidence provided by the manufacturers who identified a new data source demonstrating that the fear of hypos resulted in a loss of utility of up to 4.7%. Whilst we are aware that there is no obligation to include this data in section four of the guidance, we feel it would add value as it allows the effect of fear of hypos to be quantified.

We thank the Committee for their recommendation and look forward to receiving the Final Appraisal Determination in due course.

Yours sincerely,

[redacted]

References

1 UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patient with type 2 diabetes (UKPDS 33). Lancet 352:837-853, 1998.

2. UK Prospective Diabetes Study (UKPDS) Group. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). Lancet 352:854-865, 1998.